PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference RFW/B45319	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/09151	International filing date *(day/month/year)* 15.08.2003	Priority date *(day/month/year)* 16.08.2002
International Patent Classification (IPC) or both national classification and IPC B65D51/00		
Applicant GLAXOSMITHKLINE BIOLOGICALS SA et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of Invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18.02.2004	23.11.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Rodriguez Gombau, F Telephone No. +49 89 2399-6046

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/09151

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

2-13, 15-17	as originally filed
1, 14	filed with telefax on 24.09.2004

Claims, Numbers

1-16	filed with telefax on 24.09.2004

Drawings, Sheets

1/4-4/4	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-16
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-16
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-16
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item V.

v.i The Present application relates to the solution of three different problems:

The problem to be solved by the first invention (claims 1-13) is to facilitate the opening of a closure system for a vial. The feature which solves this problem is the upper wall of the cover part having a segment linked to the remainder of the cover part by a frangible link.

The problem to be solved by the second invention (claims 14-15) is to minimize the tendency of surface tension and capillary effects to cause residual liquid content in the vial to become trapped between the closure and the interior surface of the vial. The feature which solves this problem is the interior-facing surface enclosing an angle of 120 - 160° with the interior surface of the vial neck immediately below the plug part.

The problem to be solved by the third invention (claim 16) is to increase the stability of a vial with closure. The feature which solves this problem is a ring-shaped body having an inner perimeter adapted to engage with the base of the vial.

FR-A-2516480, which is considered to represent the most relevant state of the art, discloses a vial with a clamp part over its elastomer closure, and with a peel-off cover over a central aperture in the clamp part.

Since none of the cited documents show a solution to the above-mentioned problems, the subject matter of claims: 1 (closure system for a vial), 11 (method of closing a vial), 12 (method of filling a vial), 14 (vial closure) and 16 (vial in combination with a stand) is considered to be both novel and inventive.

v.ii Dependent claims 2-10 being dependent on novel and inventive claim 1 are automatically deemed to be novel and inventive.
Dependent claim 13 being dependent on novel and inventive claim 12 is automatically deemed to be novel and inventive.
Dependent claim 15 being dependent on novel and inventive claim 14 is automatically deemed to be novel and inventive.

Novel Device

This invention relates to a novel device, being a closure system for vials, particularly for pharmaceutical vials, for the sterile containment of drug substance or vaccine products therein.

Drug substance and vaccine products are frequently provided in vials which are closed with an elastomer closure part through which a hollow needle can be passed, puncturing the closure part, and via which the drug substance or vaccine product may be extracted for use, optionally after reconstitution by an aqueous medium introduced into the vial via the needle. Normally such a vial has a mouth opening bounded by a flange-shaped rim, and the closure part is held in a closing relationship with the mouth opening by a flexible metal clamp part which surrounds the perimeter of the closure part and holds it tightly against the rim. Often a central area of the closure part may be punctured by the needle, and the clamp part has a removable central part, which prior to use covers this central area of the closure part, and which can be removed immediately before use. Often this central part is connected to peripheral parts of the clamp part by thin frangible links, enabling the central part to be initially connected to the peripheral parts and detached prior to use, giving tamper evidence. A problem with this known device is that it is difficult to achieve a sterile seal between the central part and closure part, so the user has to "sanitise" the central area of the closure part immediately prior to use, e.g. using an alcohol wipe.

It is also known, e.g. from US-A-2002/0023409, to provide a pharmaceutical vial having a closure part made of thermoplastic material. Such a vial can be filled using a hollow needle passed through the closure part, the needle is then withdrawn, and the small residual puncture hole may then be sealed by heat sealing, e.g. using a focussed laser beam. It is an object of this invention to improve the vial disclosed therein.

It is also an object of this invention to provide an improved vial closure system having ease of construction, assembly and reduced loss of contents.

It is an object of the present invention to provide a vial closure system which in part at least overcomes the above-mentioned problems of known closure systems,

perimeter of the aperture 36, adjacent to the upper downward facing surface 24, is also shaped to correspond with the outer profile of the upper part 23 of the closure part 20 so that the closure part 20 and the clamp part 30 mate smoothly.

It is seen that the lower surface of the clamp part 30 where this is in contact with the upper surface of the closure part 20 is profiled to match the shape of the upper surface of the closure part 20 so that the clamp part 30 and closure part 20 mate together. It is also seen most clearly from Fig. 6 that the upper surface of the clamp part 30 and the upwardly convex part of the closure part 20 are profiled to form a smooth convex shape.

Around the periphery of the upper wall 31 of the clamp part 30 is a groove 37 with which the cover part 40 engages.

The cover part 40 is in the form of a cap comprising an upper wall 41, with a peripheral skirt wall 42, at the lower extremity of which is a snap fit engagement part 43 being an inwardly directed wedge shaped lip, part lip or teeth, which can engage with the groove 37 on clamp part 30 to retain cover part 40 securely in place on clamp part 30. The cover part 40 is made of a resilient plastic material to facilitate this.

A lower surface of the upper wall 41 has a sealing ridge 44 extending downwardly therefrom. As seen looking upwards toward the lower surface this ridge 44 has a circular ring-shaped plan and is of a triangular section so that it terminates in a lower knife edge sealing edge. As the cover part 40 is held in contact with the clamp part 30 by the snap-fit parts 43, 37 the resilience of the material of the cover part 40 forces the cover part 40 against the central region 23A of the upper part 23 of the closure 20, and the ridge 44 engages with and compressibly deforms the elastomer of the central region 23A to thereby form a seal with the region 23A. A sealed enclosure 45 is thereby formed between the cover part 40 and the closure part 20. The seal between the ridge 44 and the region 23A is sufficient that contaminants such as microorganisms, virus particles etc cannot pass the seal, so the enclosure 45 can remain sterile.

The vial/closure combination 10, 20, 30 shown in Fig. 1 and 2 may be assembled as follows. Firstly the vial 10 and closure part 20 are provided, preferably in a sterile state, although the combination of vial 10 and closure part 20

Claims.

1. A closure system for a vial of the type having an upwardly-facing mouth opening bounded by a rim, the closure system comprising:

an elastomer closure part shaped to sealingly engage with the mouth opening, having a lower surface facing the interior of the vial and an opposite upper surface facing away from the vial, and capable of being punctured by a needle,

a clamp part able to engage with the vial, and able to bear upon the upper surface of the closure part to hold the closure part in a closing relationship with the mouth opening, the clamp part having an aperture therein through which a region of the upper surface of the closure part is exposed when the clamp part is engaged with the vial,

a cover part, engageable with the clamp part and/or the vial to cover the said region of the closure part.

2. A closure system according to claim 1 wherein a lower surface of the cover part facing the upper surface of the closure part when engaged with the clamp part has a sealing ridge projecting therefrom to a sealing edge that follows a closed perimeter, so that when the cover part is engaged with the clamp part and/or the vial the sealing edge engages with the closure part to form an enclosure with the closure part, at least that part of the cover part which includes the sealing ridge being removable from engagement with the clamp part and/or the vial.

3. A closure system according to claim 1 or 2 having a downwardly extending plug part which can fit into the mouth opening of the vial, and an outwardly extending peripheral flange part, a downward facing surface of which can engage with the upward facing surface of a rim of the vial mouth opening in the form of a flange.

4. A closure system according to claim 3 wherein upwardly of the flange part the closure part is upwardly convex.

5. A closure system according to any one of the preceding claims wherein at least the upper surface of the closure part adjacent to the said region is made of a thermoplastic elastomer material, so that a puncture hole formed as a result of filling the vial using a hollow needle may be sealed by thermal sealing.

6. A closure system according to any one of the preceding claims wherein the clamp part is made of a mouldable plastics material, and is engageable with the above-mentioned rim bounding the mouth opening of the vial.

7. A closure system according to any one of the preceding claims wherein the clamp part comprises an upper wall part having the aperture therein, with peripheral skirt walls extending downwardly therefrom and having snap-fit engagement parts thereon to engage with the vial.

8. A closure system according to claim 7 wherein the closure part has an upwardly convex shape, and the upper wall and the upwardly convex part of the closure part are profiled such that the upwardly convex part bulges above the adjacent upper surface of the upper wall.

9. A closure system according to any one of the preceding claims, wherein the cover part is engageable with the clamp part.

10. A closure system according to claim 9 wherein the cover part is engageable by snap-fit means with the clamp part.

11. A closure system according to any one of the preceding claims wherein the cover part comprises a cap having an upper wall and a peripheral skirt wall, and the skirt wall of such a cap has a snap-fit engagement part adjacent its lower extremity, to engage with the clamp part.

12. A closure system according to any one of the preceding claims wherein the cover part covers a central aperture in the clamp part to thereby cover the region of the closure part.

13. A closure system according to any one of the preceding claims wherein the upper wall of the cover part has a segment linked to the remainder of the upper wall and/or skirt wall of the cover part by one or more thin, frangible link which can easily be severed to allow the segment to be at least partly detached from the remainder of the cover part.

14. A pharmaceutical vial having a mouth opening closed by a closure system according to any one of the preceding claims.

15. A pharmaceutical vial having:

a mouth opening closed by an elastomer closure part shaped to sealingly engage with the mouth opening and having a lower surface facing the interior of the vial and an opposite upper surface facing away from the vial, and capable of being punctured by a needle,

a clamp part engaged with the rim of the mouth opening, and able to bear upon the upper surface of the closure part to hold the closure part in a closing relationship with the mouth opening, the clamp part having an aperture therein through which a region of the upper surface of the closure part is exposed when the clamp part is engaged with the vial.

16. A method of closing a vial, wherein:

a vial is provided being of the type having an upwardly-facing mouth opening bounded by a rim in the form of a flange having upper and lower surfaces extending transverse to its upper-lower axis.

an elastomer closure part shaped to sealingly engage with the mouth opening, having a lower surface to face the interior of the vial and an opposite upper surface to face away from the vial, and capable of being punctured by a needle is inserted into the mouth opening of the vial,

a clamp part is provided able to engage with the flange around the rim of the mouth opening of the vial by a resilient snap-fit engagement of a snap fit part of the clamp part underneath a downwardly facing surface of such a flange part, and able to bear upon the upper surface of the closure part to hold the closure part in a closing relationship with the mouth opening, and

the clamp part is engaged with the assembly of vial and closure part by said snap-fit engagement.

17. A method according to claim 16 wherein subsequent to the engagement of the clamp part with the assembly of vial and closure,

a cover part is provided, engageable with the clamp part and/or the vial to cover the closure part when so engaged, a lower surface of the cover part to face the upper surface of the closure part when so engaged, and

the cover part is engaged with the clamp part.

18. A method of filling a pharmaceutical vial, comprising the steps of:

providing an assembly of an empty vial having an elastomer closure part shaped to sealingly engage with the mouth opening and having a lower surface facing the interior of the vial and an opposite upper surface facing away from the vial, and capable of being punctured by a needle, and a clamp part engaged with the vial, and bearing upon the upper surface of the closure part to hold the closure part in a closing relationship with the mouth opening, the clamp part having an aperture therein through which a region of the upper surface of the closure part is exposed when the clamp part is engaged with the vial;

inserting a filling needle downwardly through the region of the upper wall of the closure part;

injecting a liquid medicament through the filling needle to fill the vial to a suitable extent;

withdrawing the needle to leave a residual puncture hole;

engaging a cover part with the clamp part and/or the vial to cover the said region of the closure part.

19. A method according to claim 18 wherein prior to engaging the said cover part a source of heat is directed at that part of the upper surface of the closure part where the puncture has occurred to melt the elastomer material in the immediate locality of the puncture, and to thereby seal the residual puncture hole.

20. A vial closure having a plug part which has an outward-facing neck-contacting surface which engages with the interior surface of the vial neck when the closure is in place is against the cylindrical interior surface of the vial neck, and an interior-facing surface which is exposed to the interior of the vial and which when the closure is in place encloses an angle of greater than 90° with the interior surface of the vial neck immediately below the plug part.

21. A vial closure according to claim 20 wherein the angle is in the range 120-160°

22. A vial closure according to claim 21 wherein the angle is 135° +/- 10°.

23. A stand for a vial, comprising a ring-shaped body having an inner perimeter adapted to engage with the base of a vial, the stand having an outer perimeter which extends radially beyond the outer diameter of the vial body in a direction perpendicular to the mouth-base axis direction of a vial retained therein.

24. A stand according to claim 23, in combination engaged with a vial engaged therewith.